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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/086,327	05/28/1998	PHILIPPE L. DURETTE	19965Y	8099

7590 12/31/2003

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 12/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/086,327	DURETTE ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-8,11-16 and 20-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-8,11-16 and 20-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant to the directives of the amendment filed 9/29/03, claim 22 has been amended. Claims 6-8, 11-16, 20-23 remain pending.

Applicants' arguments filed 9/29/03 have been considered and found not persuasive.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-8, 11-16, 20-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification asserts that the claimed compounds are antagonists of VLA-4 or $\alpha_4\beta_7$. However, no evidence has been provided that this is the case. As stated in *Ex parte Forman* (230 USPQ 546, 1986)and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As is evident to the skilled biochemist, structure/activity

relationships are "unpredictable". Consider the following:

- Dutta (*Journal of Peptide Science* **6**, 321-341, 2000) has examined the efficacy of various peptides in the antagonism of VLA-4/VCAM-1 binding. As stated on page 329, col 2, last two lines, the following two compounds were inactive both *in vitro* and *in vivo*:

  cyclo[Ile-Leu-Asp-Val-NH $(CH2)_2CO$]
  Ac-cyclo(Orn-Leu-Asp-Val)

  These peptides are minor variations of peptides that were active.

- Arrhenius (*USP 5,688,913*) discloses (cols 17-18) several examples of compounds which failed to antagonize VLA-4. These compounds are minor variations of other compounds that were potent antagonists of VLA-4.

- Komoriya, Akira (*J. Biol. Chem.* **266** (23), 15075-15079, 1991) discloses that in an assay of $\alpha_4\beta_1$ activity, the pentapeptide EILEV was active, but pentapeptide EILDV was not. This latter peptide differs from the former by just one methylene unit.

- Haworth, Duncan (*Br. J. Pharmacol.* **126**(8), 1751-1760, 1999) discloses various VLA-4 antagonists. At least one of the disclosed compounds was inactive; this compound differed by only a few methylene units from a compound that was active.

- Haubner (*J. Am. Chem. Soc.* **118**, 7881, 1996) discloses (table 2) two compounds which failed to inhibit fibrinogen binding to the $\alpha_{IIb}\beta_1$ receptor, and vitronectin binding to the the $\alpha_V\beta_3$ receptor. The reference also discloses (p. 7882, col 2) that replacement of glycine with alanine in RGD results in a "drastic loss" of activity. These data argue for "unpredictability" in structure activity relationships of integrins generally. In addition, the "unpredictability" in structure activity relationships of RGD-peptides has direct relevance to the claimed compounds. As disclosed in Yang Y (*European Journal of Immunology* **28** (3) 995-1004, 1998) RGD-containing peptides can bind to VLA-4. Thus, if one cannot predict structure activity relationships of RGD peptides in their binding to VLA-4, it stands to reason that such unpredictability extends to other compounds which either do bind VLA-4, or which are asserted to exhibit such an effect.

- Lin (*J Med Chem* **42** 920, 1999) discloses that removal of a single amino acid (aspartic acid) from compound 11 eliminates VLA-4 antagonistic activity.

In view of the foregoing, it is evident that VLA-4/ligand interactions are very specific, and very exacting, and above all, the structural features necessary for antagonism cannot be predicted. Accordingly, the key factor required for a finding of "undue experimentation" is firmly in place. In addition, there are no "working examples" which demonstrate that the claimed compounds can be used to antagonize VLA-4, or can be used to treat any of the disorders recited in the specification (e.g., asthma, allergies, inflammation, MS). In addition, there is no direction or guidance presented about how to use the compounds to antagonize VLA-4; there are only proposals for experiments. Thus, in view of the unpredictability of structure/activity relationships in VLA-4 antagonism, the state of the prior art, the relative skill of those in that art, and the absence of any working examples, it is evident that "undue experimentation" would be required to determine which of the compounds can be used to antagonize VLA-4 or $\alpha_4\beta_7$, or to treat a given disease. At the present time, there is no appropriate *in vitro* data. It is suggested that the term "pharmaceutical" be deleted from claim 20.

In the response filed 9/29/03, it is argued that the specification describes methods for using the compounds on pages 21-35. However, this is not accurate. On the cited pages is presented speculation as to what might happen if a skilled artisan attempted to use the claimed compounds. However, the specification does not actually teach the skilled artisan how to use the claimed compounds to antagonize VLA-4. The response (filed 9/29/03) also argues that the specification lists more than 300 names of compounds. However,

listing a compound, or describing how to synthesize it does not amount to a teaching of how to use the compound.

Next the response argues that while the references cited by the examiner do provide examples of compounds which failed to antagonize VLA-4, it is nevertheless true that most of the compounds tested were effective antagonists, and that in some cases substantial variations in structure were tolerated. It is certainly true that in each case, the authors chose to report more sucesses than "failures". It may also be true that in a few cases, significant structural alterations were tolerated without loss of activity. But it is also true that very minor changes led to the abolition of activity; in a few cases, addition or subtraction of a single methylene unit was sufficient to eliminate activity. The key issue is whether one can predict the loss, or the retention, of activity merely by viewing the structure of a compound, or a set of compounds. Clearly, one cannot. It may prove to be the case, at some point in the future, that one of the claimed compounds is a VLA-4 antagonist. Should this prove to be the case, then perhaps it will be true that a significant number of other compounds within the claimed genus will turn out to be VLA-4 antagonists as well. But as matters currently stand, there is no reason to expect that even <u>one</u> of the claimed compounds is a VLA-4 antagonist. No explanation has been provided as to how the skilled artisan could have predicted the various "failures" of compounds in the cited references to antagonize VLA-4, and none is evident. Just as the skilled artisan could not have predicted the failure of various compounds (as disclosed in the cited references)

to antagonize VLA-4, so too the skilled artisan cannot predict efficacy of the claimed compounds to antagonize VLA-4.

In view of the absence of guidance presented, the absence of working examples, the nature of the invention, the state of the prior art, and the unpredictability of the art, it is clear that "undue experimentation" would be required to practice the claimed invention.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

✺

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

D. Lukton 12/23/03

CHRISTOPHER S. F. LOW
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